2/10/98
ORIGINAL

THIN-FILM INTRACORTICAL RECORDING MICROELECTRODES

Quarterly Report #3

(Contract NIH-NINDS-NO1-NS-7-2364)

October - December 1997

Submitted to the

Neural Prosthesis Program
National Institute of Neurological Disorders and Stroke
National Institutes of Health

by the

Center for Integrated Sensors and Circuits
Department of Electrical Engineering and Computer Science
University of Michigan
Ann Arbor, Michigan
48109-2122

January 1998

Thin-Film Intracortical Recording Microelectrodes

Summary

The goal of this contract is to develop a family of active recording probes suitable for fundamental studies in neurophysiology and for use in neural prostheses. The probes will have 64 sites of which 8 can be selected for use by the external world. The sites will be buffered on-chip. On one probe the neural signals will then be passed directly off chip, whereas on the other the signals will be amplified, multiplexed, and then passed off chip to minimize external leads. Both two-dimensional (2D) and three-dimensional (3D) configurations of these probes are being developed.

During the past term, significant progress has been made in several areas. We have continued to fabricate passive probes for a variety of users and have begun experiments on chronic recording from 3D passive structures using the "brain-in-a-box" probes. The first such implant survived in guinea pig auditory cortex for one month but after this time the implant channels became open circuits due to what appears to have been a cable break. This is being investigated. Nonetheless, these are the first passive 3D recordings done over an appreciable period of time.

We have explored the signal attenuation present on our mounted 2D acute probes. Typical signal attenuation is about four percent for these structures with a worst-case level of about 10 percent, depending on the site impedance. These levels are primarily set on-chip by the probe design and should be very uniform from channel to channel on a multichannel probe. Interchannel crosstalk, on the other hand, should be negligible on the probe itself, increasing to about 1.8 percent when the interchannel capacitance associated with output leads and the "stalk" printed circuit board are included. Thus, a 500μV spike on one channel would couple into an adjacent channel as a 9μV signal. The use of on-chip circuitry should elimiknate this coupling.

The first neural signals have been recorded using a probe with on-chip buffers and multiplexers and an externally-supplied clock. This was an acute structure used in guinea pig auditory cortex. Some residual clock feedthrough after demultiplexing was noted, yielding a noise level of about 50μV, but most of this noise was subsequently shown to be related to the relatively high output impedance of the buffer stage used (15KΩ). Other buffers, which have significantly lower output resistances, should reduce this noise to less than 20μV and hence be transparent to typical recording situations.

We have also begun designing the circuitry needed to accept power and site selection data for the probes over a telemetry link and then telemeter the neural signals back to the outside world, eliminating the present percutaneous connector and the supradural cable. The multiplexed neural signals will be digitized using a successive-approximation analog-to-digital converter, encoded via pulse-code modulation, and then transmitted via bipolar phase-shift keying.

During the coming term, we will perform more 3D chronic implants. will begin chronic implants with active probes, and will further explore the performance of multiplexed active probes in-vivo. We will also begin the final design optimizations for the high-end probes PIA-2 and -3 and will complete the system design for the probe telemetry system.

Thin-Film Intracortical Recording Microelectrodes

1. Introduction

The goal of this program is the realization of batch-fabricated recording electrode arrays capable of accurately sampling single-unit neural activity throughout of volume of cortical tissue on a chronic basis. Such arrays will constitute an important advance in instrumentation for the study of information processing in neural structures and should also be valuable for a number of next-generation closed-loop neural prostheses, where stimuli must be conditioned on the response of the physiological system.

The approach taken in this research involves the use of solid-state process technology to realize probes in which a precisely-etched silicon substrate supports an array of thin-film conductors insulated above and below by deposited dielectrics. Openings in the dielectrics, produced using photolithography, form recording sites which permit recording from single neurons on a highly-selective basis. The fabrication processes for both passive and active (containing signal processing circuitry) probe structures have been reported in the past along with scaling limits and the results of numerous acute experiments using passive probes in animals. In moving to chronic implant applications, the major problems are associated with the probe output leads, both in terms of their number and their encapsulation. The probe must float in the tissue with minimal tethering forces, limiting the number of leads to a few at most. The encapsulation of these leads must offer adequate protection for the megohm impedance levels of the sites while maintaining lead flexibility.

Our solution to this problem has involved two steps. The first has been to embed circuitry in the probe substrate to amplify and buffer the signals and to multiplex them onto a common output line. Using this approach, signal levels are increased by factors of about 300, impedance levels are reduced by four orders of magnitude, and the probe requires only three leads for operation, independent of the number of recording sites. A high-yield merged process permitting the integration of CMOS circuitry on the probe has been developed, and this circuitry has been designed and characterized. The second step has involved the development of silicon-based ribbon cables, realized using the same probe technology, to conduct the neural signals to the outside world. These cables have shown significant advantages over discrete leads, both in terms of the ease with which chronic implants can be assembled and in terms of the ability of the cables to survive long-term biased soaks in saline. The cables can be built directly into the probes so that they come off of the wafer as a single unit, requiring no joining or bonding operations between them. The cables are also significantly more flexible than previously-used discrete wire interconnects.

This contract calls for the development of active probes for neural recording. A 64-site 8-channel probe with site selection and signal buffering but no multiplexing is in development as is a high-end multiplexed version of this device that includes gain. During the past quarter, work has concentrated in several areas: 1) we have begun a series of experiments to record neural activity chronically using passive 3D electrode arrays; 2) we have revisited a model of the passive probes in tissue to better define signal attenuation and crosstalk, with special application to the use of mounted passive arrays, especially those using simutaneous stimulation and recording or using signals from multiple sites to improve signal-to-noise ratios; 3) we have used our low-end buffered probes with on-chip multiplexing and an off-chip-supplied clock to multiplex, transmit, and demultiplex neural signals for the first time; and 4) we have begun work to replace the percutaneous plug with a telemetry link. Work in these areas is discussed in the following sections.

2. *Passive Probe Developments*

During the past quarter, we performed an implant in guinea pig auditory cortex with the "Brain-in-the-Box" probe and obtained the first chronic recordings from a platform-based structure. As described in the last report (#2), this is a 3-D structure which is constructed from a single cable that forks off into two separate probes that are unfolded and inserted into slots in a platform, resulting in the site-sides of the probes facing one another. Although this particular device design would be fully populated with 32 sites, the prototype version only has 12 connected sites due to percutaneous connector limitations. An SEM of the front-end of the structure is shown in Fig. 1. For this implantation, a vacuum pick mounted on a micromanipulator was used to introduce the device into the brain.

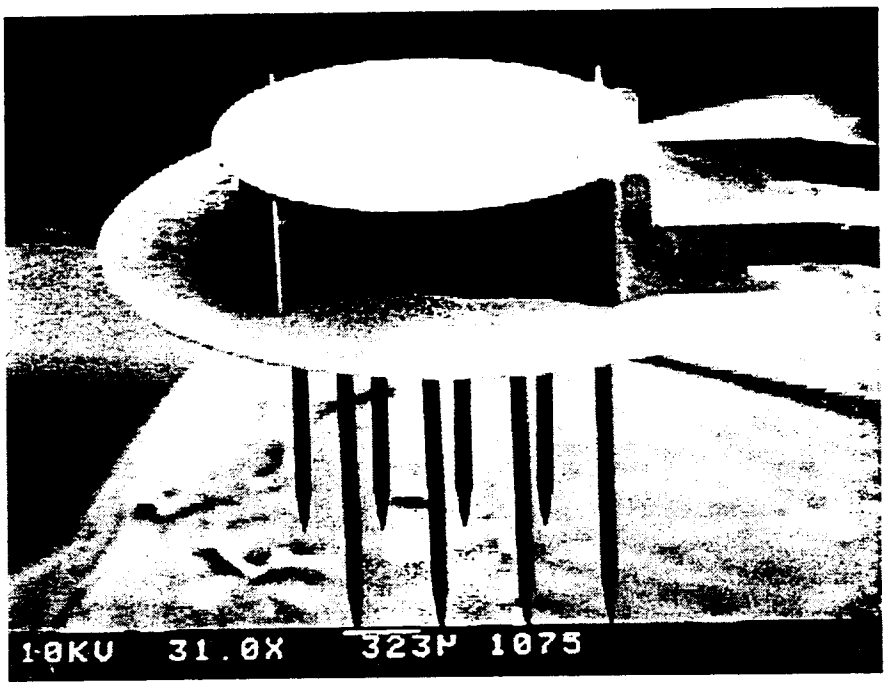

Fig. 1: The 3-D structure known as "Brain in the Box." The two cable strands which are integrated into the probes converge into a single main cable, resulting in the the two probes having sites which face one another. The shanks on this probe are spaced at 300μm.

The first recordings from this implant, taken one week postop, are shown in Fig. 2a. The units were driven with a 100msec noise burst with a 24msec repetition rate. Discriminable units are evident on channels 5 and 7, while evoked potentials are present on other channels. Three weeks later (one month postop) the recordings in Fig. 2b were obtained with the same stimulus. Here, channel 1 appears to be the only channel with units, although channel 2 periodically showed activity as well.

As described in previous quarterly reports and in presentations by our group[1] and others[2,3], we have in the past been able to rejuvenate recordings by passing a small amount

---

[1]J. F. Hetke, D. J. Anderson, J. A. Wiler and B. M. Clopton, "Chronic Multichannel Recording from Guinea Pig Inferior Colliculus." *Abstracts, 1992 Association for Research in Otolaryngology*, St. Petersburg, Feb. 1992.

of current through the sites (1μA biphasic, 10μsec/phase) or by biasing the sites with a DC voltage which is current limited though a large series resistor. We attempted this technique at this time with channel 5 in an effort to rejuvenate the activity seen one week postop. The bias was applied in 0.25V steps up to 1.5V; however, the activity did not improve on this or any other channels. In fact, activity disappeared on all channels, even those which were not biased (all but channel 5). On checking the impedances and CVs, it became evident that channels 1-4 and 9-12 had become open circuits. Looking at the site map for this probe (Fig. 3), one can see that these channels are all fed from one fork of the cable, indicating that this was probably the point of failure. We are unsure of the exact cause of this problem but perhaps movement of the probe with respect to the point of the cable's entry into the dental acrylic occurred during a quick movement of the animal's head. This device may be particularly vulnerable to breakage due to the bends which the cables must make to produce the desired structure.

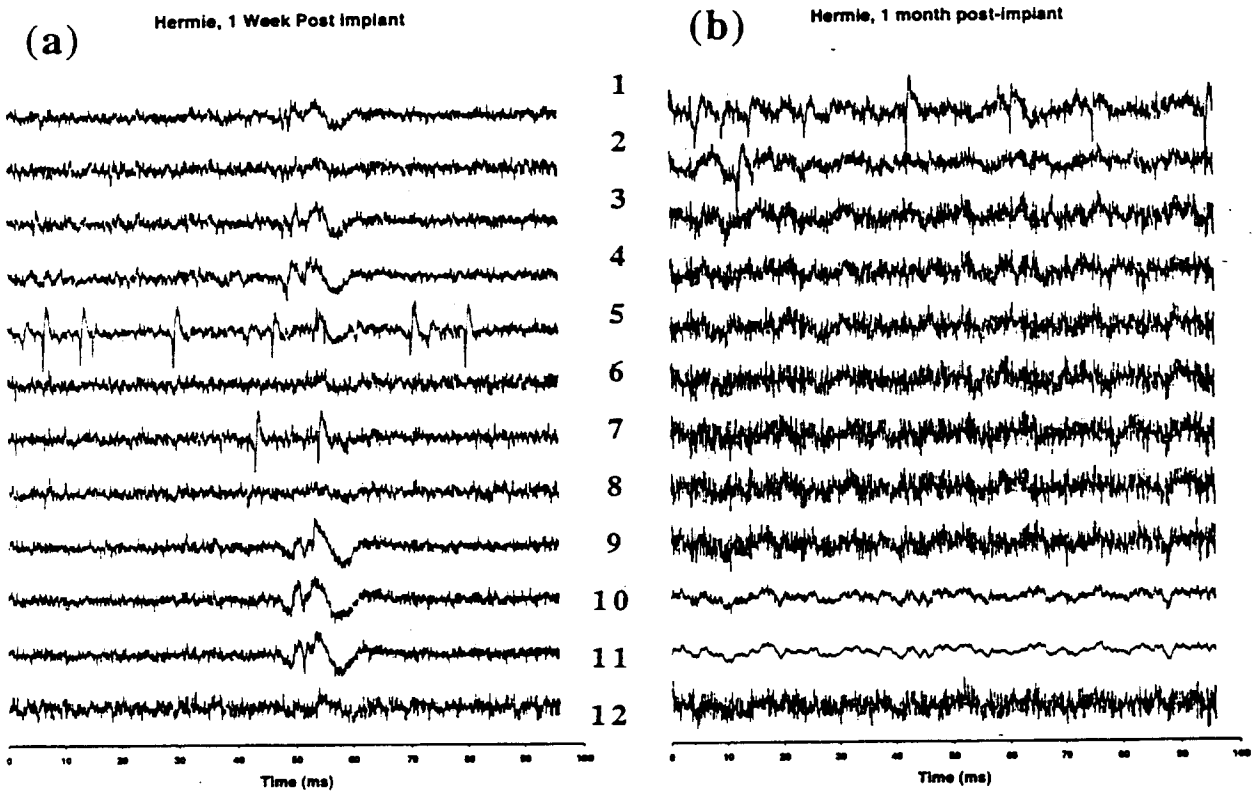

Fig. 2: Chronic recordings from a Brain in the Box probe. In (a), recordings taken 1 week postoperatively are shown. These recordings were driven by noise bursts. The noise level here is approximately 30μV. One month postoperative recordings are shown in (b). While channel 1 now has a unit, the other channels have degraded and have a higher background noise level (~50μV). Note that in this record, channels 10 and 11 were inadvertently disconnected.

---

[2]E.M. Schmidt, W.J. Heetderks and D.M. Camesi, "Chronic Recording from Cortical Areas with Multicontact Silicon Microprobes," *Abstracts, 1993 Society for Neuroscience*, Washington D.C., Nov. 1993.

[3]E. Schmidt, "Recording Properties of Thin-film Electrodes," *25th Neural Prosthesis Workshop*, Bethesda, Oct. 1994.

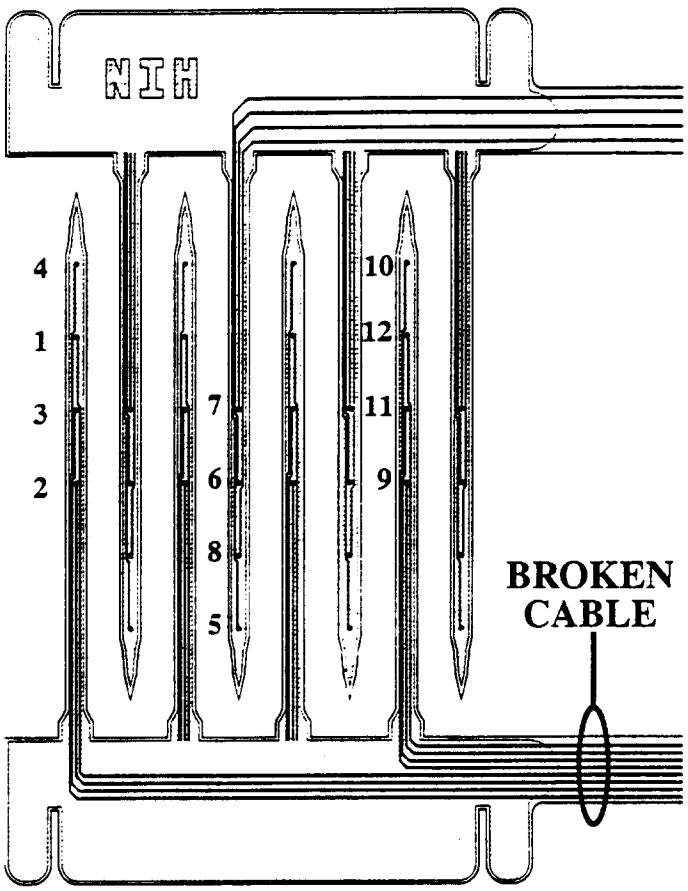

Fig. 3: Site map for Brain in the Box design used for chronic recordings. It is evident from the impedances that one of the legs of the cable broke. The other remains intact.

In this implant, the device was inserted, a chamber was constructed out of dental acrylic, and the space surrounding the probe was filled with sterile agar solution. The portion of the cable between the connector and the forked region was covered with dental acrylic. We are going to be investigating alternative methods for stabilization and closure in the coming months. Items of particular interest include new silicone elastomers available through World Precision Instruments (Kwik-Sil™ and Kwik-Cast™) which claim to have low toxicity and the ability to cure in minutes at room temperature. A material such as this could potentially be used either to stabilize the platform on the brain surface or to fill the space around the implant within the chamber. We will also continue to evaluate the remaining four sites on the existing preparation for their ability to chronically record.

3. *Passive Probe Characterization*

As probes are increasingly used for multi-channel multi-unit recording, it is becoming ever more important to thoroughly understand the charcteristics of these probes as they are used. The interchannel coupling is particularly important, especially in situations involving simultaneous stimulation and recording on the same probe or those in which signals from multiple sites are combined in order to improve signal to noise ratios. During the past quarter we have taken a close look at this situation for the acute "stalk" mounted probes we and others have been using for multi-channel recording. The study characterized the impedance properties of mounted recording probes using both 1kHz impedance measurements and direct waveform recordings. The electrodes tested were of the "CN1.2" design, with unactivated iridium sites. A few of the probes had unopened recording sites; that is, the insulation was not removed over the electrode pads. These probes offered a special opportunity to examine the coupling between electrode leads without the influence of a metal/solution interface.

Figure 4 shows a cross-section of a probe shank along with an equivalent circuit of the typical crosstalk situation where one conductor is driven and an adjacent line receives a signal from it. Nearly all of the circuit elements are capacitive although it is recognized that those capacitances associated with a solution interface may be frequency dependent and have a real part. For a probe inserted in tissue, the extracellular fluid around the probe provides a ground plane immediately adjacent to the conductors (above, C_{up}). The conductors also couple down to the probe substrate (C_{down}) through the bottom dielectrics. The probe substrate has a very large area and so is at a virtual ground with respect to the extracellular fluid even though the capacitance per unit area between the substrate and the tissue may be relatively low. The site capacitance is the dominant element in the model and is many times larger than any of the parasitics (C_{site} = 160pF for a 1megohm site at 1kHz). The interelectrode capacitance is limited, with the probe immersed, to coupling through the lateral dielectrics between the conductors. As such it is a strong function of the interelectrode spacing. For 3μm conductor lines and 3μm spaces, a 3mm long shank would give rise to calculated crosstalk of about 0.02% for a typical probe[4]. Thus, for a 500mV stimulating signal on one lead, an adjacent lead 3μm away would pick up only 100μV. For a greater spacing, cross-coupling on the probes themselves would truly be negligible. It should be emphasized that these results are based on calculations, but we believe them to be correct. On an acutely-mounted probe, however, it is unclear how much cross-coupling is present. For this situation, most of the capacitances remain those of the probe except for the crosstalk capacitance, which could be expected to increase significantly due to coupling between the output leads. No ground planes are present here. Determining the extent of this coupling was the intent of this characterization.

Figure 5 is a diagram of the CN1.2 probe layout. The sites are numbered in the order that their corresponding leads eventually connect to an external amplifier. Note that although the leads are numbered consecutively, left to right, the sites are in a different order. The impedances were measured using a commercial potentiostat and frequency response analyzer (EG&G), controlled by software running on a PC. The excitation signal was 1 kHz at a level of 5 mV. We obtained single-channel impedances with the probe lead of interest connected to the "working" electrode input, and a standard calomel electrode (SCE) and platinum foil electrode in phosphate buffer solution connected to the "reference" and "counter" inputs, respectively. During such measurements, the probes were immersed in the solution. For cross-channel impedances, we connected one of the probe leads to the

[4]K. Najafi, J. Ji, and K. D. Wise, "Scaling Limitations of Silicon Multichannel Recording Probes," IEEE Trans. Biomed. Engr., pp. 1-11, January 1990.

working electrode input and the second lead to both the reference and counter electrode inputs. These measurements were made with the probe surrounded only by air; that is, the probes were not immersed in the solution. Thus, the crosstalk capacitance measured will be with the substrate floating and will be largely the capacitances C_{down} in series together with any output lead coupling capacitance present (C_{xleads}).

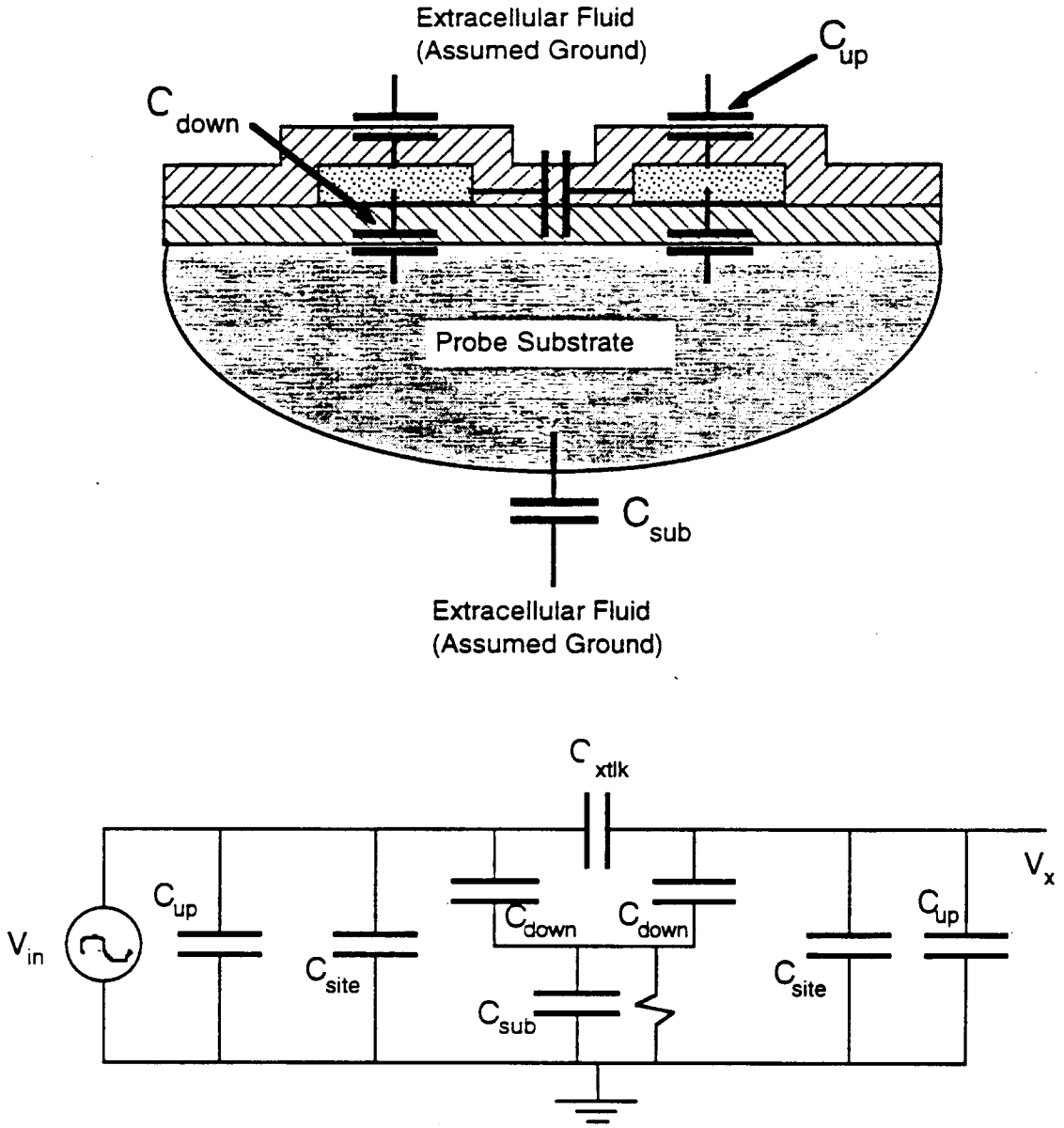

Fig. 4: Cross-section of a probe shank showing the various coupling mechanisms. The lower part of the figure shows an equivalent circuit for a crosstalk situation where one conductor is driven and the second receives the coupled signal.

The typical CN1.2 site impedance versus a counter electrode in solution was 1-3MΩ (52-160pF). This should correspond to the site impedance in parallel with C_{up} and C_{down}. Largely, it will correspond to the site impedance. The impedance of a single

unopened site, however, was found to be about 21-25 MΩ (6.6pF), with an average of 23.5 MΩ (STD = 1.2, N = 15). This should correspond approximately to C_{up} in parallel with C_{down} since C_{sub} is assumed large and C_{site} here will be very small. This corresponds to a worst-case signal attenuation of about ten percent for the 3 MΩ probe.

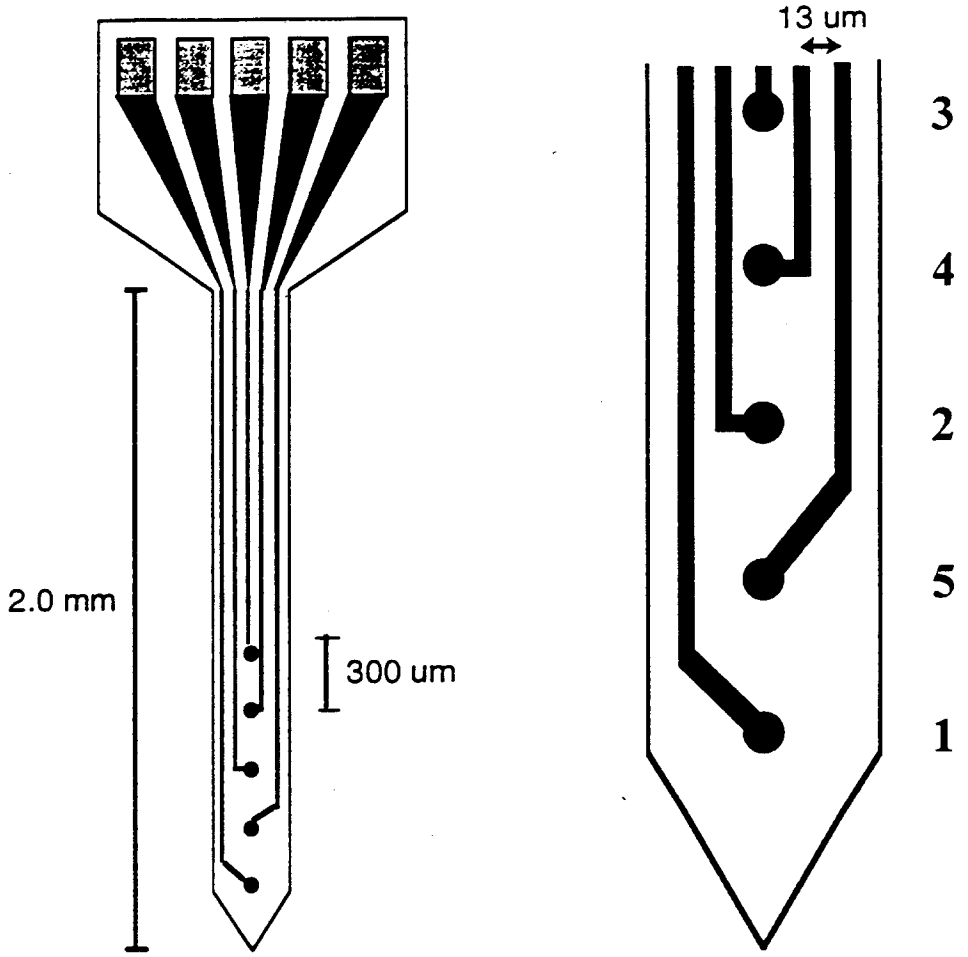

Fig. 5: Layout of CN1.2, a five-channel passive probe designed for acute recordings. The site size is 100μm^2.

Between two probe leads, the measured cross-channel impedance depends weakly on the spacing between the channel leads. This reflects the coupling through the substrate ($C_{down}/2$) plus external lead coupling (C_{xleads}). The impedance increases from 37MΩ for adjacent leads to over 50 MΩ for greater spacings, suggesting an adjacent output lead capacitance of about 1.4pF. While small, this would lead to a crosstalk at 1kHz of about 1.8 percent for a 2MΩ site. For a 500μV spike, this would couple to an adjacent electrode as about 9μV, which is below the typical noise level but perhaps not completely negligible. Figure 6 shows the overall configuration used in these measurements.

We rely on the fact that in normal operation, the silicon substrate acts as ground. Localized potentials, if coupled into the substrate, are divided against a much larger area of the substrate where no such signals are present and hence the actual substrate potential does not vary appreciably. One exception to this would be the case of a widely distributed slow-wave potential in the tissue, which might couple into the substrate. From there it would

couple through C_{down} into the channel itself, where it would be divided against the site impedance. We assessed this coupling by driving the solution and inserting the probe so that one (or more) sites was immersed while the rest were out of the solution. The signals coupled to the various channels were monitored. The electrode was a CN1.2 probe again with normal (open) sites, plugged into the same headstage. A 1kHz sinusoidal signal, generated by a voltage-to-current generator, was applied to the saline bath through a platinum foil electrode (source) and a stainless steel needle electrode (sink). The electrode was positioned such that it entered the saline solution between the source and sink electrodes of the current generator.

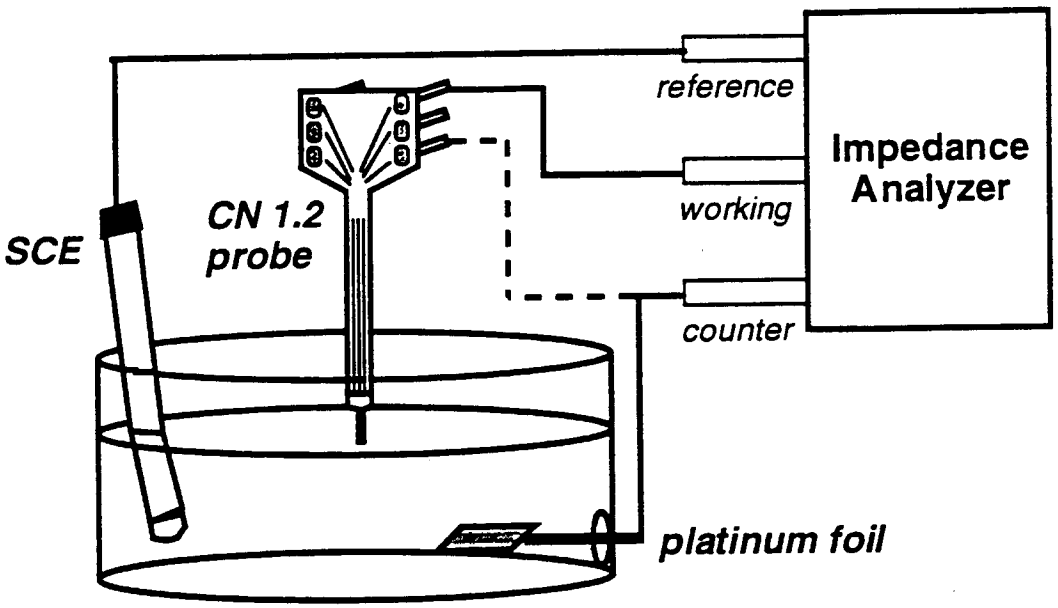

Fig. 6: General electrode arrangement for impedance measurements. For some measurements, the counter lead was connected to a second channel but for most the configuration was as shown in solid lines.

In this arrangement, the channel that was immersed received the local signal at the probe, while the sites that were not immersed received a signal indirectly via the probe substrate. In order to provide a pathway to ground, the channels that were not immersed were connected to ground at the headstage using 1megohm resistors (approximately the 1kHz impedance of the electrode-solution interface). The signal coupled into the channels from the substrate was about 4% of the full signal in this case, representing the portion of a very diffuse tissue potential that would be coupled from the substrate. Since the sites would presumably be recording directly from tissue, this is a small perterbation on the primary signal being seen anyway.

Another situation of interest that can be assessed from Fig. 4 is that of a probe coated with parylene with the sites opened using ablation. In this case, assuming good adhesion of the parylene to the probe substrate, the substrate-solution capacitance (C_{sub}) would be considerably reduced, as would C_{up}. In this case, signal attenuation on a given channel might improve marginally (perhaps from 5 percent to 3 percent, for example) but interchannel crosstalk would degrade considerably (e.g., from 0.02% to perhaps 2% on the probe itself, excluding output leads and assuming the substrate capacitance becomes negligible (which it might not). In this case it is particularly important to include a top

ground contact to the substrate on the probe so that the substrate remains grounded and does not float to allow crosstalk to occur.

Even for mounted probes, the observed signal attenuation is not significant and the crosstalk between leads is acceptable for recording situations. For combinations of recording and stimulation, however, it is not, and on-chip circuitry would required to suppress coupling on the output leads. In addition, on active probes using off-chip clocks, it remains to be seen if adequate clock suppression can be achieved. Some encouraging experiments in this regard are reported in section 4 of this report.

3. *Active Three-Dimensional Recording Probe Arrays*

Developing a family of active recording probes suitable for fundamental studies in neurophysiology and for use in neural prostheses is the goal of this program. It is increasingly clear that for either of these applications, large numbers of sites (>100) are required in order to make significant progress. This implies that active multiplexing circuitry be located on the probe so that the number of external leads required for access to these sites is tractable. Thus, a continuing emphasis in this program has been to develop the technology and circuit designs to permit this on-probe circuit integration. As reported in the past quarterly reports, we have made significant recent progress toward this goal, both in the development of a high-yield fabrication process as well as in the design and testing of the resulting 2D and 3D active probes.

There have been several important recent accomplishments in the area of process development. The process now consistently yields a low contact resistance on all sorts of contacts, including circuit contacts, recording sites, and bonding pads. The contact problem had been primarily responsible for low yields experienced with active probes such as PIA-2. We have also developed a technique for ensuring that the active probes are released properly in EDP without having their circuit areas being undercut. This technique is based on the use of deep-etched slots around the shanks and wings of the active probes so that these areas are released solely by the front-side silicon etch, leaving thick silicon under the circuit areas. Using dielectric bridges for corner compensation at the outer corners of the circuit areas is also important in protecting the circuit areas from what would otherwise be very rapid EDP undercutting at these corners. Other process problems that have been resolved include improving the coverage of LTO over circuit metal; improving the adhesion of gold lead transfers on the 3D arrays; and the use of high-quality dielectric passivation over the interconnection leads to minimize signal attenuation as well as noise coupling. The full active probe process has now been run successfully with high yield; the active probes realized by the process are being used for testing both in-vitro and in-vivo. The first active 3D probe array has also been created by microassembling the finished 2D active probes.

The current set of active recording probes was developed to finalize designs of the analog circuit blocks required on the larger PIA-2 and -3 probes and to explore the use of an off-chip clock with these probes. In multi-probe 3D arrays, an off-chip clock is required to allow sychronization of outputs and yet will require suppression of the 5V signals to below 20μV, a ratio of 250,000:1 (4ppm). The current probes include several different buffers and amplifiers along with 4:1 multiplexing. The extensive evaluation of these circuit blocks in terms of power, area, noise, and gain, and the detailed study of issues such as dc baseline stability, multiplexer clock noise, and the role of the bias applied to the probe substrate, will be very valuable in optimizing the designs for larger and more complicated active recording probes (PIA-2 and -3) later this spring. We have now tested a number of this new set of fabricated active probes in-vitro and in-vivo; the circuit functions are consistent with their design targets. In the last quarterly report, we presented successful in-vivo recordings using one of the buffered probes, the probe "BUF1". Each shank of the probe had two recording sites separated by 24μm center-to-center. One site passes directly off the probe (passive), while the other is buffered on-chip by a source follower. In recording from isolated neurons with several of these probes in several passes on two animals, consistent results have been obtained. The noise performance with active channels is not inferior (and actually appears somewhat superior) to that of the passive channels. This is significant, indicating that on-chip signal processing is possible without compromising signal-to-noise ratios.

During the past quarter, we have explored the critical questions surrounding the use of an off-chip clock with these active probes. We successfully recorded single-unit spike activity in guinea pig auditory cortex using our multiplexed probe "MUX1". This is the first time that isolated neurons have been recorded through multiplexed signal channels on-chip and then demultiplexed off-chip. It is also the first that we have used an off-chip clock with such a multiplexer. The experiments have demonstrated that on-chip multiplexing is feasible, as is the use of an external clock.

As there is more and more demand for multi-site recording microelectrodes and large 3D probe arrays, it is increasingly attractive to build active probes so that external lead counts can be reduced by multiplexing the recording channels and so that sites can be selected that are close to active neurons. The most serious potential problem associated with multiplexed probes is noise. Compared to probes without the multiplexing function, there are a number of additional noise sources. One is clock switching noise, which could feed into the multiplexed channel through the parasitic capacitance associated with the MOS multiplexing switch. Noise could also feed through the power supply lines and p-n junctions due to the current spikes resulting from clock transitions. Another potential noise source involves direct coupling of the clock itself into the output line. This could be the major noise source when an external clock is used. A third possible source is the aliasing problem; that is, frequency components (either signal or noise) higher than the multiplexing frequency can be down-shifted into the lower frequency band, resulting in signal distortion or additional low frequency noise. Since the neural signals of interest extend down to amplitudes well under 50μV, all these noise problems pose a significant challenge in designing active multiplexed probes.

In order to overcome these noise problems, care must be exercised in both circuit design and layout. Generally speaking, the on-chip circuitry must have very low output resistance, must provide a high power supply rejection ratio, and should amplify the signal and well as limit its bandwidth before multiplexing. In laying out the circuitry, it is very important to minimize the resistance of power supply leads; to ensure good low-resistance contacts to the substrate, p-wells, and n-pockets; to route interconnects in such a way that noise coupling can be minimized; and to build complimentary switches if possible to cancel switching noise feedthrough. Also, the external demultiplexing system is very important. It must have very low overall noise, provide bounce-free power supplies, and have sharp cut-off filters to suppress high-frequency clock/sampling noise.

Among the active probes that have been designed and fabricated, there are four designs of multiplexed probes. Two of these provide amplification as well as bandwidth limiting, while the other two do not. Three of the designs offer power supply rejection while the fourth does not. And the designs also have different output resistances. However, all of the designs use an external clock. As discussed previously, it is challenging to use an off-chip clock, because it requires clock noise suppression of 10ppm or better. An external clock is required to allow clock synchronization in multi-probe 3D arrays. It also simplifies both the probe circuitry and the external demultiplexing system.

The probe "MUX1" is the simplest design among the four multiplexed probes. As illustrated in Fig. 7, it consists of voltage buffers, a two-bit counter, and CMOS switches. The buffer is a simple source follower, the same as that used in the probe "BUF1". The counter is made of static d-type flip-flops (Fig. 8), which are designed to reduce switching noise in the middle of the sampling window. As shown in Fig. 9, the counter is fully functional. The use of a CMOS switch has two advantages over a single-channel MOS transistor. The first is that the dynamic analog-signal range in the ON state is greatly increased. The second is that since the n- and p-channel devices are in parallel and require opposing address signals, the feedthrough due to the address change is at least partially

cancelled. This probe was very carefully laid out; in particular, separate n-pockets were used to isolate the digital and analog circuitry so that noise coupling could be minimized through the p-n junctions during the clock transitions. The overall buffer-multiplexer (4:1) circuit has been tested and shown to work completely (Fig. 10).

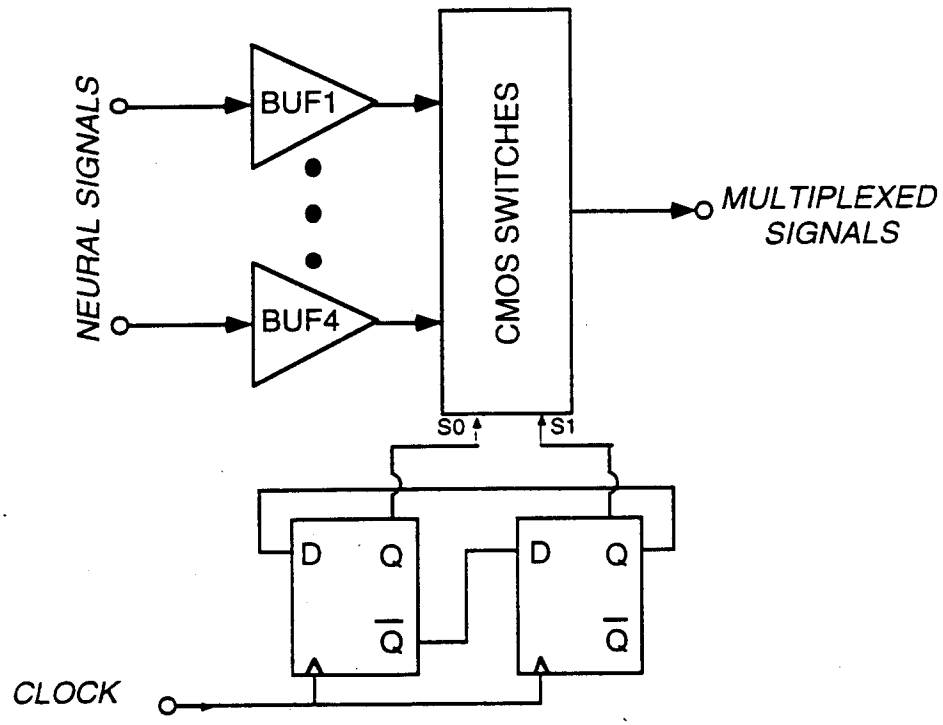

Fig. 7: Block diagram of the active probe "MUX1".

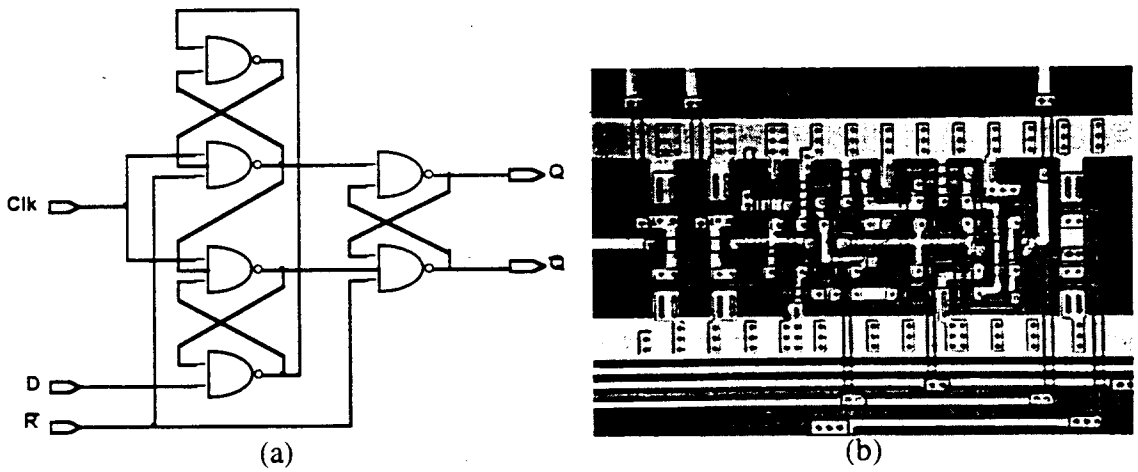

Fig. 8: a) Schematic diagram of the d-type flip-flop; b) Picture of the d-type FF.

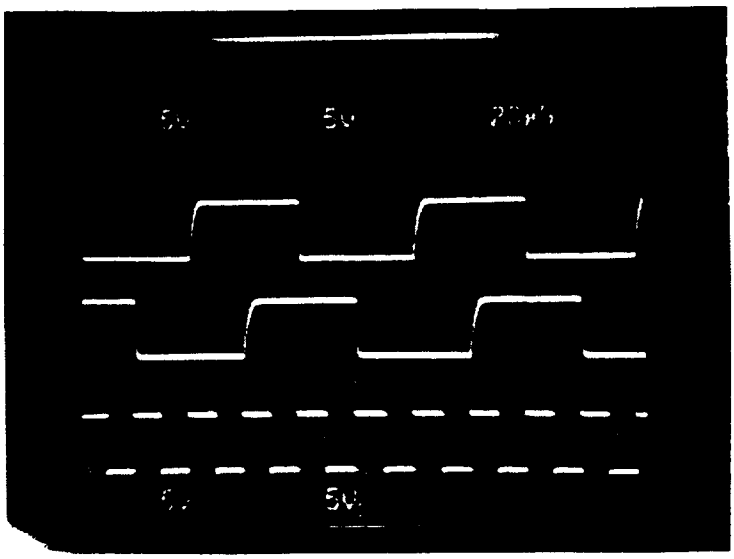

Fig. 9: Outputs of the counter on "MUX1". The top two traces are the two-bit address signals of the counter, and the bottom one is the clock.

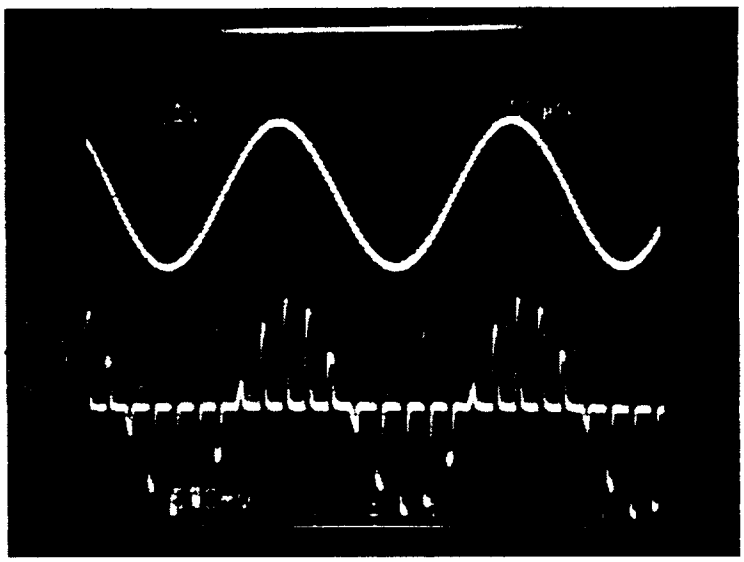

Fig. 10: The multiplexed output (bottom) of the probe "MUX1" versus the input signal (top). As can be seen from the output, one of the four input channels has a 5kHz sinusoid signal, and the other three are grounded. The clock has a frequency of about 200kHz.

Figure 11 is a system diagram of the probe "MUX1" and its external electronic circuitry, and Fig. 12 is a schematic of the external demultiplexing system that has been built for use with these probes. Since an off-chip clock is used, the demultiplexing circuit is far simpler than that for PIA-2, where an on-chip clock was used and where a frame marker was inserted in the output signal to allow external clock reconstruction. The demux system contains three stages: a first amplification stage, the demultiplexing stage, and a second amplification/filtering stage. Because the neural signals are multiplexed without any amplification on the buffered probes, the first amplifier in the demultiplexing system should provide as much gain as possible to avoid further noise. The gain of this stage is limited by the bandwidth and the speed of the op amp used, as well as by any dc-bias variations on

the buffered channels. In this case, the gain of the first-stage amplifier is 20x. The crucial part of the demultiplexing stage is to set proper sampling window, including a suitable delay time and sampling duration. With the right sampling window, the recovered signals can avoid most of the ripples associated with the clock transitions. Figure 13 shows the enable address generated by the sampling control circuit --- a dual monostable timer. Here, a 200kHz non-symmetrical (20% duty cycle) clock is used. With a clock frequency of 200kHz, the system should be able to sample up to 16 channels if the signal bandwidth is limited to 6kHz. A non-symmetrical clock is used to prevent switching noise from occurring in the middle of the sampling window. Also, a 2μs delay and a 2μs sampling duration are set by the two pairs of capacitors and resistors, C41-R41 and C42-R42, respectively. The second-stage amplifier further boosts the demultiplexed signals. The low pass filter (LPF) would ideally eliminate all of the high frequency noise. Therefore, it should have a high stop-band rejection and good selectivity. On our external electronics board, two LPFs are used in serial to provide such performance. The overall gain-phase spectrum of the demultiplexing system is shown in Fig. 14. It has total gain of 5000x (74 dB), a lower cutoff frequency of 50Hz, and a high cutoff frequency of 5kHz. The equivalent input noise of this system is less than 5μV.

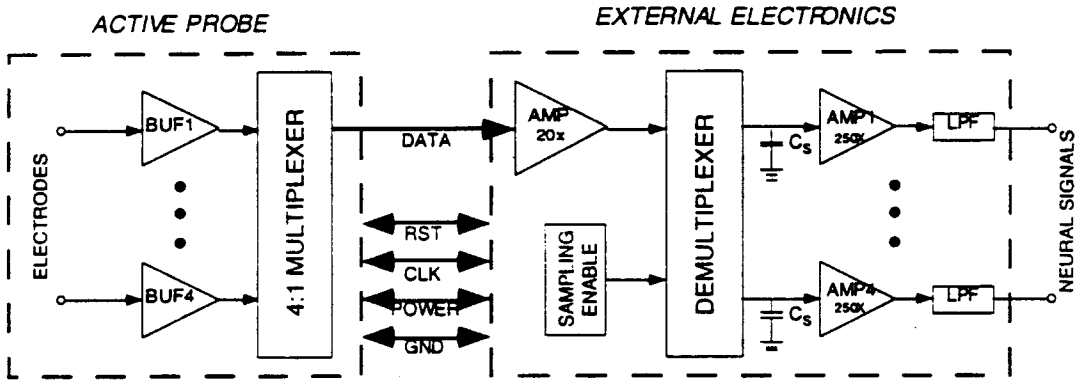

Fig. 11: System diagram of the probe "MUX1" and its external demultiplexing electronics.

It should be mentioned that the probe "MUX1" actually represents the "worst case scenario" of the active multiplexed probes. First, the output resistance of the source follower is the highest among our three buffered designs, in the range of 10-20k-ohms. At this resistance level, the signal output is still susceptible to high-frequency noise to some extent. Second, the gain of the buffer is less than one (0.8~0.9). Third, the buffer does not provide any power supply rejection, which means it does not immune to any clock-induced power supply bounce. The frequency response of the source follower is also very wide; as a result, the multiplexer may have some aliasing problems. In summary, this probe represents a worst case in terms of noise pickup. However, "MUX1" is a simple and robust design. And more importantly, it can help us to identify the noise sources and paths in the multiplexing system. If "MUX1" has reasonable noise performance, then the other probes should do still better.

During the past quarter, we used this simplest of the multiplexed probes, "MUX1", to successfully record isolated neural signals from guinea pig auditory cortex in acute experiments. The recorded neuron activity shown in Fig. 15 was driven by white noise bursts. This is the first time that an active multiplexing-demultiplexing probe system was used to record single-unit neural signals. It is also the first time that external clock has been used to successfully record neural activity.

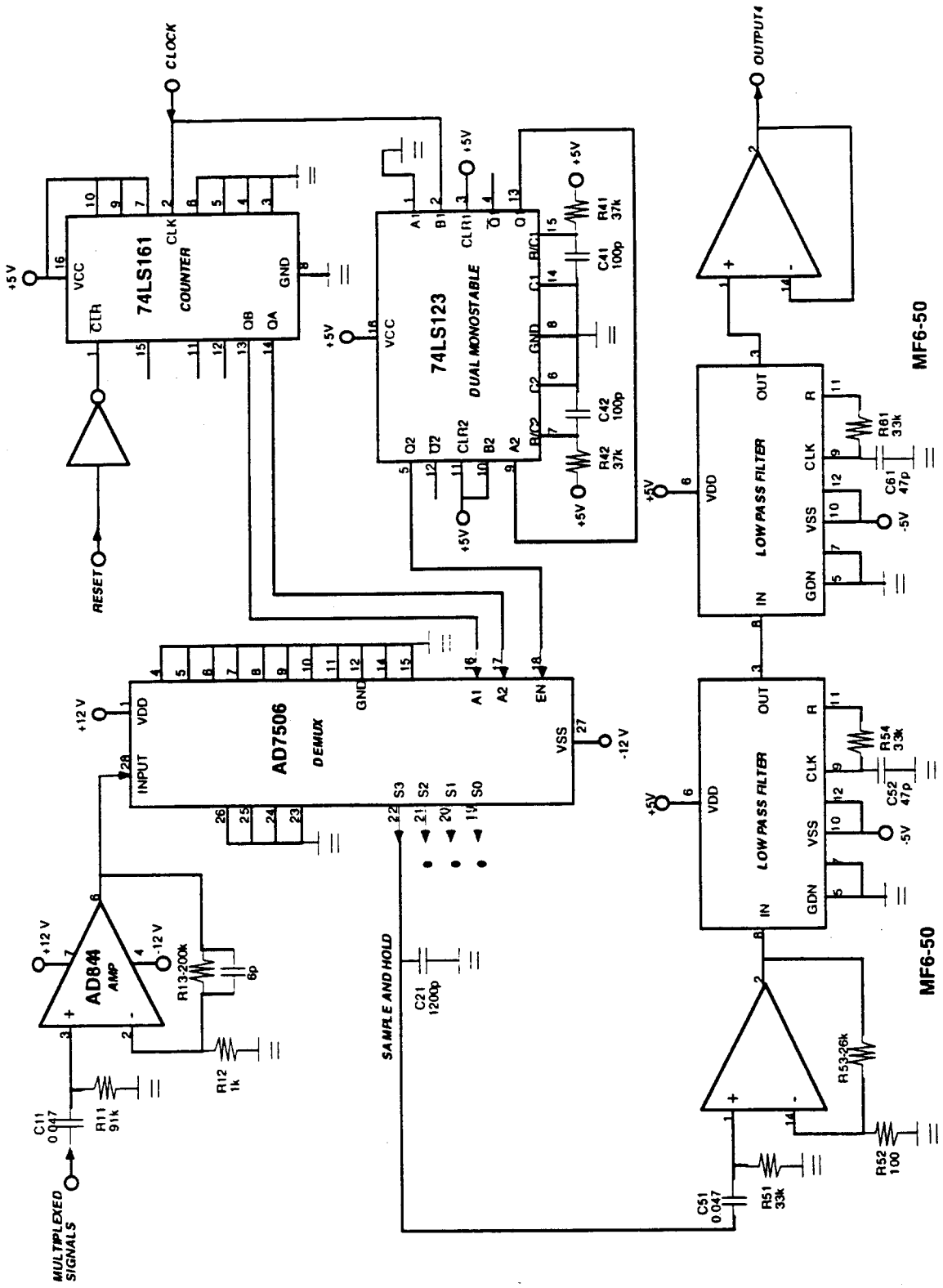

Fig. 12: The schematic of the external demultiplexing electronics .

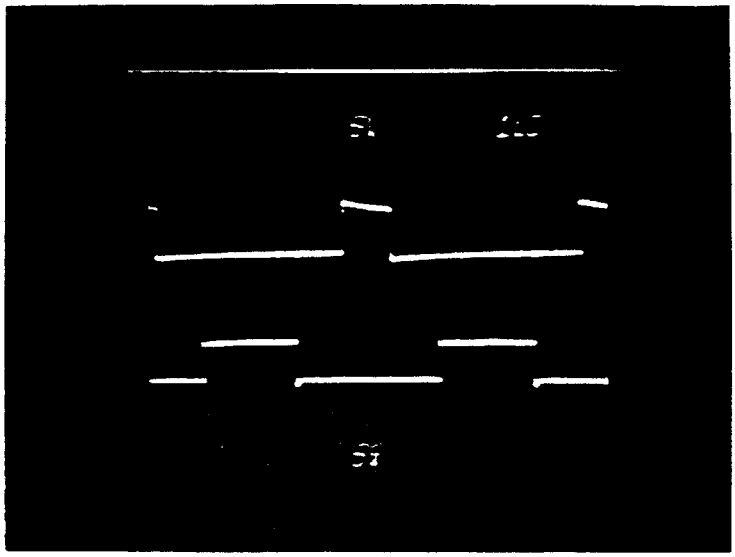

Fig. 13: The enable signal generated by the sampling window control circuit. The top trace is the 200kHz clock with a 20% duty cycle. The bottom trace is the enable address, which has a 2μs delay and 2μs duration.

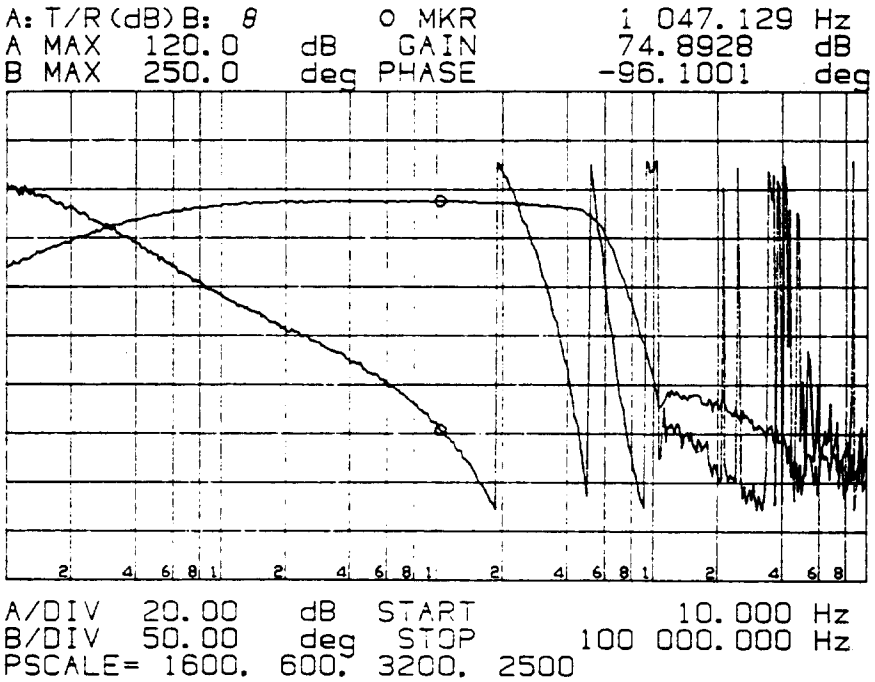

Fig. 14: The overall gain-phase spectrum of the demultiplexing system. The system provides a gain of 74dB and a pass band of 50Hz-5kHz.

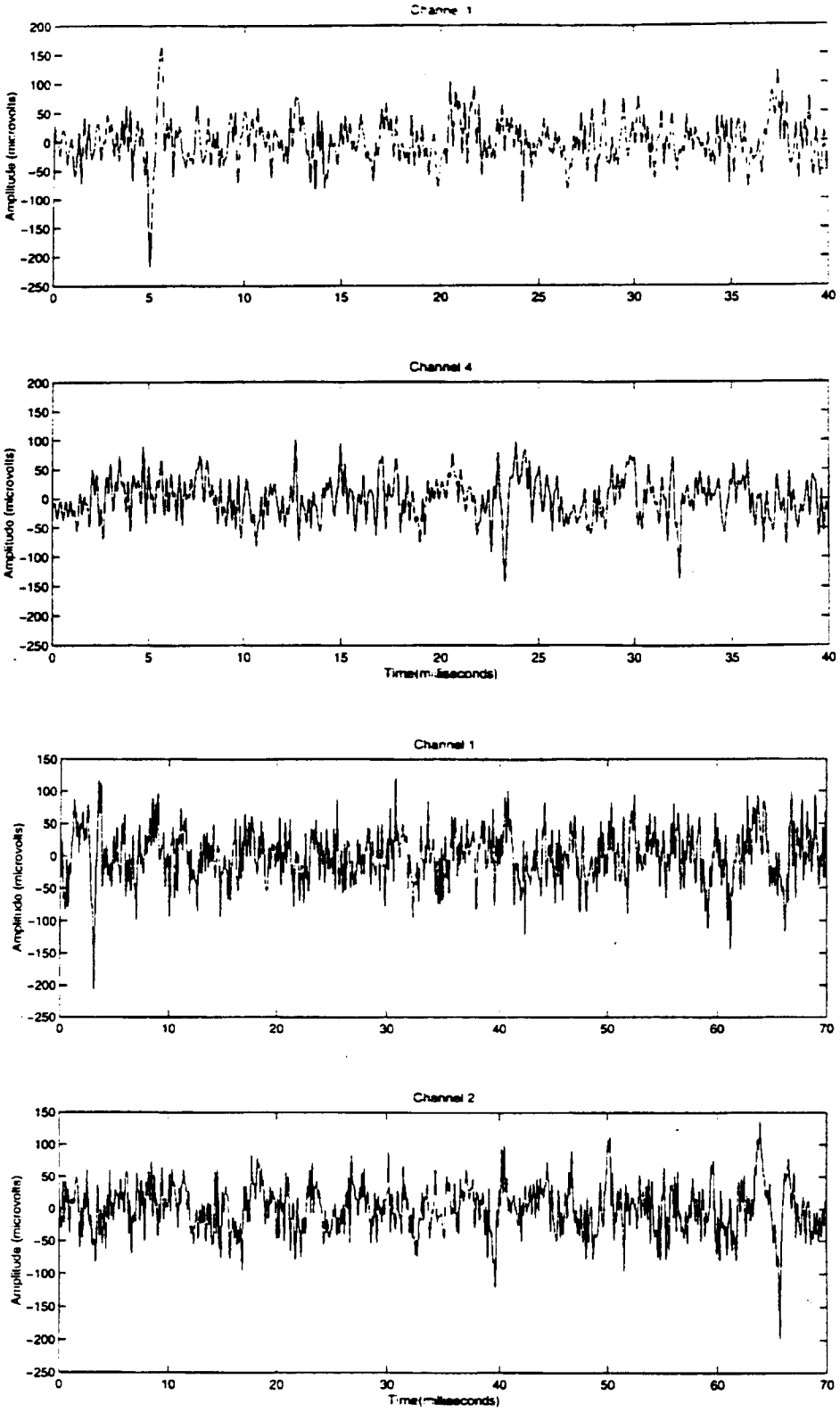

Fig. 15: Single-unit neural activity recorded using the probe "MUX1" from the guinea pig auditory cortex. The neural responses were driven by the white noise bursts.

As expected, the noise level of the recovered signals is higher than that of the non-multiplexed signals. It is typically about 50μV here. Our goal is to improve the noise performance of such probes and to study the noise sources and their possible coupling paths. In subsequent in-vitro experiments, we found that one major noise problem associated with "MUX1" is clock coupling directly through the interconnect external leads and bonding wires. As we increase the power supply from 4.5V to 6V, the output resistance of the source follower is reduced: the coupled noise level over this range was cut by about a factor of two. As discussed before, at the present output resistance level, the signal is indeed susceptible to noise coupling. Our theoretical calculations also support this conclusion. Noise feedthrough at the circuit level does not appear to be a primary noise contributor at this point; we see no significant noise difference when the clock to the on-chip multiplexer is turned off. There is one significant noise component that we have not yet been able to identify. It has one particular frequency component that is less than 200Hz.

The results from these in-vivo and in-vitro experiments are very promising. It is a simple matter to increase the bias current and/or the transistor size of the source followers in future designs in order to reduce the output resistance and thus the crosstalk noise of these chips. There is still room to improve the performance of the external electronics as well. For example, the first stage of the amplifier should be moved to the headstage, next to the multiplexed outputs. The low cutoff frequency in the demux system can be increased, and a bounce-free power supply can be provided to the probe. Adding a further delay to the sampling window may be necessary: and the sampling duration may need to be somewhat narrower than used in the above experiments. Based on the performance of "MUX1", we believe that the other multiplexer designs will have very good performance. During the coming quarter, we will continue the testing and experiments with the other active probe designs. Work will also proceed on the design of the larger active probes defined by the current contract.

5. An Implantable Telemetry Interface for Recording Probes

Over the last quarter, a preliminary overall system architecture for the telemetry link and the associated circuitry for use in fully implantable microprobes has been developed. The main thrust of this system is the use of encoded digital signals that will be transmitted from an implanted chip using an active transmitter that operates at a frequency of at least 25MHz. The active multichannel microprobes previously designed in this program have had directly-wired outputs using three leads - Power, Clock and Ground. The proposed system will use an inductive telemetry link to achieve reliable power and data transfer to and from the implanted device. This circuitry could be integrated on a surface platform or, based on our recent work with microstimulators, could be integrated on the probes themselves.

The block diagram of the proposed system is shown in Fig. 16. As can be seen, for a system of 32 recording sites (as in the current version of PIA-2), the sites on the probe are functionally grouped into 8 groups of 4 sites each. The signals from the 32 sites (in groups of 4) are sent to a set of 8 four-to-one multiplexers. These can be implemented using either a shift register or operating the switching array with the control signals generated by a decoder in the front end. Of the four signals that are supplied to a particular multiplexer only one can be selected. This feature constrains the system in that the number of possible combinations of sites is reduced to 65,536 (4^8). However, this arrangement provides two advantages:

1. It simplifies the data transfer protocol and hence the bandwidth requirements of the telemetry link.

2. More importantly, it permits site scanning and zooming. This enables the operator to select those areas that show the most interesting activity and "zoom" into the appropriate sites.

The eight selected signals are multiplexed using an 8:1 MUX in PIA-2. The MUX (which uses a TDM scheme) will be operated at 160kHz. The multiplexed signals, in the future system, will then be digitized using an analog to digital converter (ADC). A variety of digitizing schemes have been studied for this application. These architectures include --- flash , algorithmic, sigma-delta and successive approximation. A successive approximation converter has been chosen for the proposed system. Successive approximation will be used because it satisfies the tradeoffs relating to speed, accuracy, resolution, and simplicity of the circuit. Due to the high frequencies at which the ADC is to be run, it will be necessary to modify the converter architecture by including a sample and hold circuit. The S/H amplifier will be connected to the ADC and will ensure speed compatibility between the ADC and the transmitter. Successive approximation designs are also desirable because they can be designed for low power dissipation, which in turn will permit the incorporation of more than one ADC per system to improve bandwidth and speed. This issue will be studied in more detail as we proceed with the design of the first complete prototype system. Since the redesigned PIA-2, -3, -2B, and -3B probes will all be 64-site 8-channel devices, the front-end selector will change but the multiplexer and output ADC/transmitter circuitry will be as shown.

The digitized signal will be encoded in pulse code modulation. A number of encoding schemes have been evaluated in terms of required bandwidth, ease of encoding (power dissipation), and energy-to-noise ratio. Of these, the energy-to-noise ratio is the most important since it directly affects the probability of error (and hence, the reliability of the reverse telemetry link). The reason pulse code modulation was chosen is that it has a high degree of robustness and a high energy-to-noise ratio. Furthermore, PCM lends itself to such data compression features as companding. It is expected that such features will facilitate more on-chip signal processing that can be done in future. It has also been decided to use a bipolar scheme for encoding since it will reduce the DC component of the transmitted signal.

The penultimate stage in the reverse telemetry process is the modulation of the encoded signal prior to transmission. A bipolar phase-shift keying (BPSK) scheme has been chosen for this purpose because it ensures a low probability of error and is more reliable than other amplitude-based schemes such as ASK. The energy-to-noise ratio of BPSK is about 3dB lower than ASK for equivalent systems. Finally, the modulated signal will be transmitted by an on-chip active transmitter that operates at least at 25MHz. A high carrier frequency of 25MHz was chosen since: 1) it minimizes the possibility of noise interference and crosstalk between the transmitted signal and the received signal; and 2) it ensures speed compatibility between the ADC and the transmitter.

For the forward (input) telemetry, a Class E amplifier is being tested. A prototype of this amplifier has already been built and is in the process of being tuned and optimized for operation at 4MHz. This will be the frequency of operation for the forward telemetered signals. Tests have been performed on the Class E amplifier to characterize it in terms of received power as a function of radial and spatial distance from a receiving coil.

Over the next quarter, all of the outstanding issues and trade offs associated with this system will be resolved and we will begin designing and simulating the circuitry.

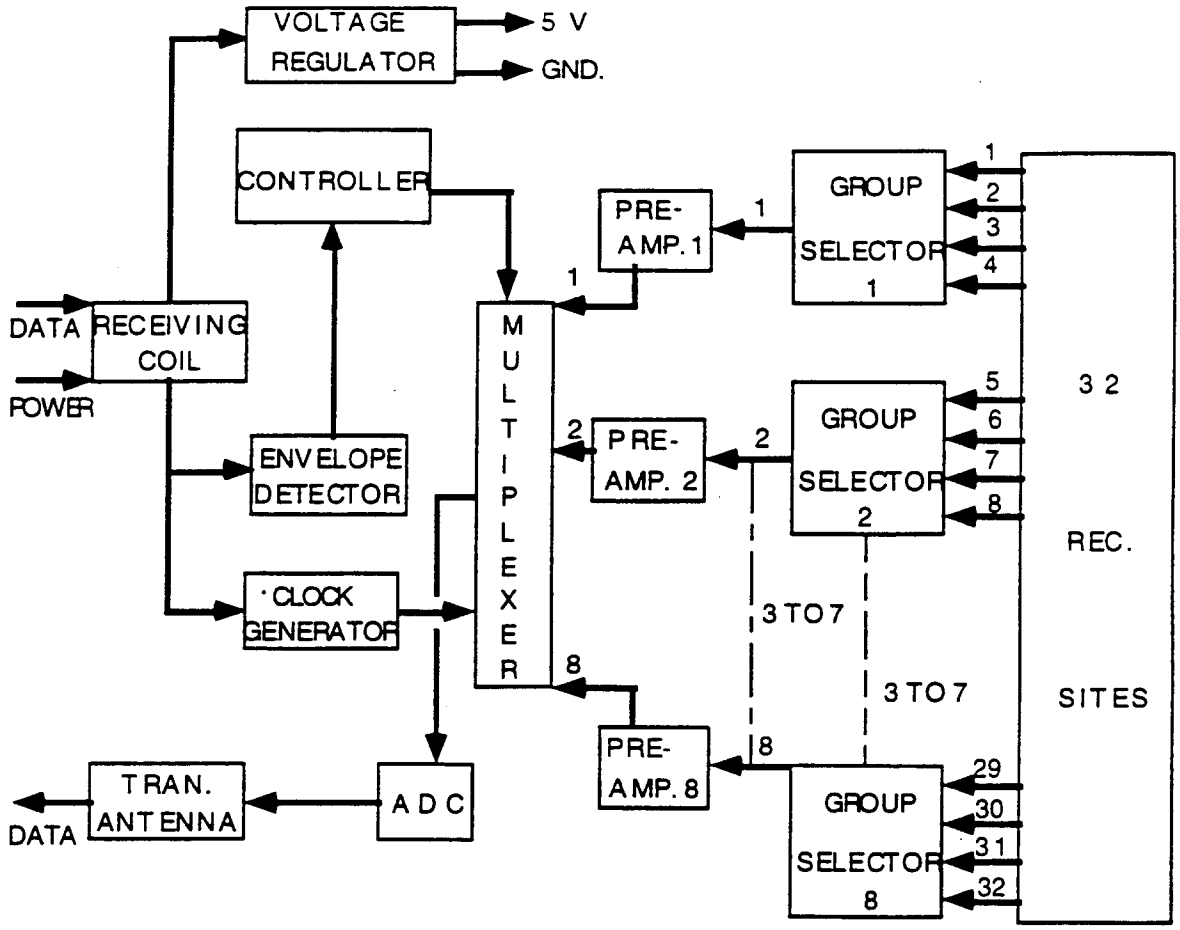

Fig. 16: Schematic representation of the telemetry link and the on-chip circuitry for fully implantable multichannel microprobes.

5. Conclusions

The goal of this contract is to develop a family of active recording probes suitable for fundamental studies in neurophysiology and for use in neural prostheses. The probes will have 64 sites of which 8 can be selected for use by the external world. The sites will be buffered on-chip. On one probe the neural signals will then be passed directly off chip, whereas on the other the signals will be amplified, multiplexed, and then passed off chip to minimize external leads. Both two-dimensional (2D) and three-dimensional (3D) configurations of these probes are being developed.

During the past term, significant progress has been made in several areas. We have continued to fabricate passive probes for a variety of users and have begun experiments on chronic recording from 3D passive structures using the "brain-in-a-box" probes. The first such implant survived in guinea pig auditory cortex for one month but after this time the implant channels became open circuits due to what appears to have been a cable break.

This is being investigated. Nonetheless, these are the first passive 3D recordings done over an appreciable period of time.

We have explored the signal attenuation present on our mounted 2D acute probes. Typical signal attenuation is about four percent for these structures with a worst-case level of about 10 percent, depending on the site impedance. These levels are primarily set on-chip by the probe design and should be very uniform from channel to channel on a multichannel probe. Interchannel crosstalk, on the other hand, should be negligible on the probe itself, increasing to about 1.8 percent when the interchannel capacitance associated with output leads and the "stalk" printed circuit board are included. Thus, a 500μV spike on one channel would couple into an adjacent channel as a 9μV signal. For on-chip circuitry, the coupling should be eliminated.

The first neural signals have been recorded using a probe with on-chip buffers and multiplexers and an externally-supplied clock. This was an acute structure used in guinea pig auditory cortex. Some clock feedthrough after demultiplexing was noted, yielding a noise level of about 50μV, but most of this noise was shown to be related to the relatively high output impedance of the buffer stage used (15KΩ). Other buffers, which have significantly lower output resistances should reduce this noise to less than 20μV and hence be transparent to typical recording situations.

We have also begun designing the circuitry needed to accept power and site selection data for the probes over a telemetry link and then telemeter the neural signals back to the outside world, eliminating the present percutaneous connector and the supradural cable. The multiplexed neural signals will be digitized using a successive-approximation analog-to-digital converter, encoded via pulse-code modulation, and then transmitted via bipolar phase-shift keying.

During the coming term, we will perform more 3D chronic implants, will begin chronic implants with active probes, and will further explore the performance of multiplexed active probes in-vivo. We will also begin the final design optimizations for the high-end probes PIA-2 and -3 and will complete the system design for the probe telemetry system.